Drug-Drug Interactions among Kidney Transplant Recipients in The Outpatient Setting

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ABSTRACT

Background: Number of patients undergoing kidney transplantation is ever increasing. Drug-drug interactions (DDIs) can complicate transplant patient's treatment course.

Objective: To investigate patterns and factors associated with potential DDIs in kidney transplant recipients under maintenance immunosuppressive regimen at a referral transplantation center in Shiraz, Iran.

Methods: 390 eligible kidney transplant outpatients referred to Motahhari clinic and one of the attending nephrologist's private office during an18-month period were assessed for DDIs. Using the Lexi-Interact online drug interactions software, the prescribed drugs were assessed for the number and type of potential DDIs. Only type D and X interactions were considered eligible for inclusion.

Results: During the study period, 344 DDIs were detected of which, 290 were type D; 54 were type XDDIs. 81% of the detected DDIs were pharmacokinetics. Interaction between cyclosporine + mycophenolic acid (32.3%) was the most frequent DDIs followed by cyclosporine + atorvastatin (11.3%). Immunosuppressant (43.44%) was the most frequently used medication responsible for DDIs. Number of co-administered medications (OR: 1.34, 95% CI: 1.12–1.51) and cyclosporine as main immunosuppressive main drug (OR: 10.43, 95% CI: 6.24–17.42) were identified as independent risk factors for DDIs.

Conclusion: Major DDIs were common in kidney transplant recipients. Considering the importance of DDIs in kidney transplant patients, more attention is warranted in this regard by health care members, especially physicians and pharmacists.

KEYWORDS: Kidney transplantation; Drug interactions; Immunosuppressive agents; Outpatients

INTRODUCTION

Kidney transplantation is an appropriate therapeutic option for patients with end-stage renal disease (ESRD). It is the only option for many patients. Number of patients undergoing kidney transplantation is growing every day. Solid organ transplantation in Iran began as early as 1967 with a kidney transplantation in Shiraz, southern Iran [1]. A total of 34,166 kidney transplantations (4436 and 29,730 grafts from cadaver and living donors, respectively) were performed up to the end of 2012 in Iran. In 2011–12, Iran had ranked first in performing deceased-donor kidney and liver transplantations among all countries in the Middle East Society for Organ Transplantation (MESOT) [2]. According to the latest literature from 1988–2003, 1200 kidney transplantations were performed in Shiraz [3].

Drug-drug interactions (DDIs) are an important class of medication errors [4], which is common among both hospitalized and outpatients. DDIs can prolong a patient's hospitalization and impose additional costs on the health care system [5]. A DDI can be defined

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as a phenomenon that occurs when the clinical effects or pharmacokinetics of a drug is altered by a prior administration or co-administration of another drug [6, 7]. Adverse DDIs could lead to increase hospital admissions, length of hospitalization and could impose a cost of approximately US$ 1 billion annually to the health care system [8, 9].

Kidney transplant recipients consume several medications simultaneously including immunosuppressive agents and other medications for managing the underlying or new-onset diseases, such as diabetes, hypertension and dyslipidemia [10, 11]. Hence, clinical conditions of patients, which is sometimes progressive and life-threatening, characteristics of their co-morbidities, number of prescribed medications, frequent hospitalizations, and their effects on patient's quality of life requires more attention to detect probable DDIs and their associated factors. Also, these patients are at risk for acquiring opportunistic infections, which may need to consume antimicrobial agents which could lead to DDIs. Although, it is not well studied, cohorts, case series, and case reports demonstrated that DDI in this population are present and many cautions should be considered in pharmacotherapy of kidney transplant because drug interaction could lead to many serious adverse drug reactions [12-14]. A cohort study conducted in kidney transplant recipients, shows that almost 40% (5 out 13) of patients would be admitted due to a probable adverse drug reaction [15]. Therefore, due to immunosuppressive narrow therapeutic window, which could be affected by DDIs, and the importance of immunosuppressive medications interactions, which could lead to graft rejections, we conducted this study with the objective of determining the patterns and associated factors of potential DDIs in kidney transplant outpatients under maintenance immunosuppressive regimen.

MATERIALS AND METHODS

Setting

This cross-sectional study was conducted in Mottahari Outpatient Clinic, affiliated to Shiraz University of Medical Sciences, southern Iran, and one of the attending nephrologist's private office from September 2015 to February 2017. The Medical Ethics Committee of Shiraz University of Medical Sciences approved the study protocol; all patients or their legal guardian gave informed written consent prior to their inclusion in the study.

Patient Selection

All adult patients (≥18 years of age) who had received kidney transplant with stable renal function under maintenance immunosuppressive regimen plus one or more non-immunosuppressive medications were recruited. Patients with unstable serum creatinine within the last three months were excluded. Those who had received kidney transplant previously or had concomitant pancreatic or hepatic transplantation were also excluded from the study. There was no limitation regarding previous acute rejection episodes in including patients.

Data Collection and Drug Interaction Screening

Demographic as well as clinical data (age, sex, donor type, duration of transplantation, reason for chronic kidney disease, underlying diseases and co-morbidities, type of dialysis before transplantation, and duration of dialysis before transplantation), and laboratory data (serum creatinine, blood urine nitrogen [BUN], aspartate transaminase [AST], alanine transaminase [ALT], alkaline phosphatase [ALP], and bilirubin) were collected during the 18 months by a pharmacist under the supervision of an attending clinical pharmacist. All the medications that the patients had consumed, such as immunosuppressive and non-immunosuppressive drugs, were recorded. As-needed and herbal medications were not considered. All the above data were collected through a face-to-face interview with patients as well as reviewing their medical charts in the clinic or the private office.

DDIs screening was performed by the Lexi-Interact™ online software. According to this software, DDIs are classified into five classes—A, B, C, D, and X—based on their sever-

Table 1: Lexi-comp drug interaction software classifications definition of drug-drug interactions for severity and reliability rating

Classification	Definition
Severity	
Major	The effects of interaction might result in death, hospitalization, permanent injury or therapeutic failure.
Moderate	The effects of interaction might require medical interventions.
Minor	The effects of interaction would be considered tolerable in most cases and does not need medical interventions.
Reliability rating	
Excellent	Multiple randomized clinical trials or single randomized clinical trial plus more than two case reports
Good	Single randomized clinical trial plus less than two case reports
Fair	More than two case reports or less than two case reports plus other supporting data; or a theoretical interaction based on known pharmacology

ity and clinical relevance. Therefore, we just investigated and considered D or X category interactions that have more clinical importance [16]. Table 1 lists the definition of severity and reliability rating of DDIs by the Lexi-Interact software.

Pharmaceutical interactions, defined as chemical and/or physical incompatibilities between two drugs or dosage forms when mixed with each other, were not analyzed since they were not within the scope of the study and also were not supported by the Lexi-Interact software. Medication classes involved in the interactions were categorized by the Anatomical Therapeutic Chemical (ATC) classification system, and the defined daily dose (DDD) index 2017 by the World Health Organization (WHO) collaborating center for drug statistics methodology [17]. Based on the definitions used in Riechelmann, *et al* [18], and Hadjibabaie, *et al* [19], studies, hepatic and renal impairments were defined as an increase of ≥10% in the mean plasma levels of hepatic enzymes (AST≤35 U/L, ALT≤40 U/L, ALP≤110 U/L, or bilirubin ≤22 μmol/L as the normal range) and serum creatinine level (≤1.1 mg/dL as the normal range).

Statistical Analysis

Examination of normal distribution for continuous variables was performed by one-sample Kolmogorov-Smirnov test. Normally and non-normally distributed continuous variables were expressed as mean±SD and median (interquartile range [IQR]), respectively. Qualitative variables were expressed as percentage. Comparison between parametric and non-parametric continuous variables was performed by *Student's t* test for independent variables and Mann-Whitney U test, respectively. χ^2 or Fisher's exact tests, when appropriate, were used for analyses of categorical variables.

To assess the possible association between the incidence of D or X DDIs and different variables, we performed a logistic regression analysis with a stepwise method. DDI was taken as the dependent variable. First, variables including age, sex, duration of therapy, underlying disease, type of dialysis before transplantation, duration of dialysis before transplantation, donor type, number of medications, immunosuppressive main drug, and organ dysfunction were separately entered into univariate logistic regression analysis. Then, each independent variable with a p value <0.05 was considered for multivariate logistic regression analysis. Each variable with a p value <0.05 was found as a risk factor for detected DDIs. A p value <0.05 was considered statistically significant. All statistical analyses were performed with SPSS® for Windows® ver 20 software (IBM company, New York, NY, United States).

Table 2: Demographic and clinical features of the studied population (n=390)

Variable	Value
Sex	
Male (%)	265 (67.9)
Female (%)	125 (32.1)
Age (yrs)	
Mean±SD	45±13
Range	18–72
Donor type	
Related living (%)	54 (13.8)
Non-related living (%)	63 (16.2)
Cadaveric (%)	273 (70.0)
Cause for end-stage renal disease	
Hypertension (%)	97 (24.9)
Diabetes (%)	41 (10.5)
Others* (%)	252 (64.6)
Type of dialysis before transplantation	
Hemodialysis (%)	361 (92.6)
Peritoneal dialysis (%)	26 (6.7)
No dialysis (%)	3 (0.7)
Duration of dialysis before transplant (months)	
Median (IQR)	12 (15)
Range	0–120
Duration of immunosuppressive therapy (months)	
Median (IQR)	40.5 (17.8)
Range	1–264

*Unknown cause, nephrolithiasis, polycystic kidney disease, post-streptococcal glomerulonephritis, infections, autoimmune disease, reflux, hyperuricemia, glomerulonephritis, adverse drug reaction.

RESULTS

During this study, 421 patients were screened, amongst whom 31 were excluded due to either receiving no non-immunosuppressive medication (n=21) or concomitant pancreatic or hepatic transplantation (n=10), leaving 390 individuals for analyses.

Demographic and clinical features of the population are summarized in Table 2. More than 60% of the participants were male. Seventy percent of the patients received deceased donor kidney. Hypertension was the cause of ESRD in about one-fourth (24.9%) of the participants. Hemodialysis was the most common type of dialysis before transplantation. Twelve immunosuppressive regimens were used in this study. The most frequently used immunosuppressive regimen was tacrolimus + mycophenolic acid + prednisolone (Table 3).

The median (IQR) number of medications used by each patient was 6 (3). Three most frequently used immunosuppressant drugs were prednisolone (33.6%), mycophenolic acid (31.5%), and tacrolimus (19.8%). The most frequently prescribed on-immunosuppressant medications were amlodipine (14.4%), calcitriol (9.8%), and atorvastatin (8.2%). During the study period, we detected 344 DDIs, of which 290 (84%) and 54 (16%) were class D and X interactions, respectively. One hundred and six (27.2%), 48 (12.3%), and 19 (4.9%) patients had at least one, two, and three DDIs, respectively. More than three simultaneous DDIs were detected in 21 participants (5.4%).

Regarding mechanism, 84% and 16% of DDIs were pharmacokinetics and pharmacodynamics, respectively. Reliability rating of all the detected DDIs was as follow: good (70.05%), poor (26.16%), and excellent (3.79%).

Table 4 shows the characteristics for the 10 most frequently detected DDIs in the study population. Cyclosporine + mycophenolic acid interaction (32.3%) followed by cyclosporine + atorvastatin (11.3%), prednisolone + calcium (10.5%), and mycophenolic acid + calcium (10.3%), respectively. Almost half (49.1%) of all detected DDIs were between two immunosuppressant medications. The remaining 36.1% and 14.8% of DDIs were between one immunosuppressant and non-immunosuppressant medications and between non-immunosuppressant agents, respectively. Atorvastatin as cause of most prevalent type X interactions were used by 26.7% of patients by a mean±SD daily dose of 19.2±7.7 (range: 10–40) mg/day.

Immunosuppressant (43.4%), systemic corticosteroids (22.5%), and calcium channel blockers (10.30%) were the three most frequently used

Table 3: Immunosuppressive regimens used in the study population (n=390)

Regimen	n (%)
Tacrolimus + Mycophenolic acid + Prednisolone	223 (57.2)
Cyclosporine + Mycophenolic acid + Prednisolone	131 (33.6)
Cyclosporine + Azathioprine + Prednisolone	12 (3.1)
Sirolimus + Mycophenolic acid + Prednisolone	7 (1.8)
Tacrolimus + Azathioprine + Prednisolone	6 (1.5)
Cyclosporine + Prednisolone	4 (1.0)
Mycophenolic acid + Prednisolone	2 (0.5)
Cyclosporine + Everolimus + Prednisolone	1 (0.3)
Everolimus + Prednisolone	1 (0.3)
Sirolimus + Azathioprine + Prednisolone	1 (0.3)
Tacrolimus + Everolimus + Prednisolone	1 (0.3)
Tacrolimus + Mycophenolic acid	1 (0.3)

Table 4: Class, probable mechanism, severity, reliability rating, and frequency of the 10 most prevalent class D and X drug-drug interactions in the study population

Drug-Drug interaction	Probable mechanism	Class	Severity	Reliability rating	n (%)
Cyclosporine + Mycophenolic acid	Cyclosporine-mediated inhibition of biliary excretion of MPGA† via the MRP2‡ transporter.	D	Moderate	Good	126 (32.3)
Cyclosporine + Atorvastatin	Inhibition of CYP3A4 and OATP1B1§-SLCO1B1¶ mediated uptake of atorvastatin by cyclosporine	X	Major	Good	44 (11.3)
Prednisolone + Calcium	The mechanism of this interaction is unknown	D	Moderate	Fair	41 (10.5)
Mycophenolic acid + Calcium	Mycophenolate apparently binds to calcium, forming a less soluble/absorbable complex	D	Moderate	Good	40 (10.3)
Tacrolimus + Omeprazole	Omeprazole inhibits the metabolism of tacrolimus	D	Major	Good	10 (2.6)
Atorvastatin + Diltiazem	Inhibition of the CYP3A4-mediated metabolism of Atorvastatin by diltiazem	D	Major	Fair	5 (1.3)
Cyclosporine + Gemfibrozil	The mechanism of this interaction is unknown	D	Major	Fair	5 (1.3)
Atorvastatin + Gemfibrozil	Inhibition of OATP1B1-SLCO1B1 mediated uptakeof Atorvastatin by Gemfibrozil	X	Major	Excellent	4 (1.0)
Allopurinol + Calcium	Calcium may decrease allopurinol absorption	D	Moderate	Good	4 (1.0)
Cyclosporine + Verapamil	Inhibition of CYP3A4-mediated metabolism of Cyclosporine by Verapamil	D	Moderate	Excellent	4 (1.0)

†Mycophenolic acid glucuronide conjugate, ‡Multidrug resistance-associated protein 2, § organic anion transporting polypeptide 1B1, ¶ solute carrier organic anion transporter 1B1

Table 5: Anatomical, Therapeutic, Chemical (ATC) classification of medication classes responsible for detected drug-drug interactions

ATC code	Medication class	Medication (s)	n (%)
L04A	Immunosuppressant	Cyclosporine, Tacrolimus, Mycophenolic acid, Sirolimus, Everolimus	755 (43.4)
H02A	Systemic corticosteroids	Prednisolone	391 (22.5)
C08C	Selective calcium channel blockers with mainly vascular effects	Amlodipine	179 (10.3)
C10A	Lipid modifying agents	Atorvastatin, simvastatin, Gemfibrozil	113 (6.5)
A12A	Calcium	Calcium carbonate, Calcium gluconate	49 (2.8)
J01E	Sulfonamides and trimethoprim	Sulfamethoxazole and trimethoprim	47 (2.7)
M04A	Antigout preparation	Allopurinol, Colchicine	31 (1.8)
A02B	Drugs for peptic ulcer and gastro-esophageal reflux disease	Omeprazole, lansoprazole	25 (1.4)
B03A	Iron preparation	Ferrous sulfate	21 (1.2)
C08D	Selective calcium channel blockers with direct cardiac effect	Verapamil, Diltiazem	15 (0.9)

medication classes responsible for DDIs (Table 5). Based on univariate logistic regression analysis, age (OR: 1.02, 95% CI: 1.003–1.032), donor type (OR: 0.69, 95% CI:0.52–0.90), number of co-administered medications (OR: 1.19, 95% CI: 1.08–1.31), immunosuppressant main drug (OR: 9.12, 95% CI: 5.70–14.60), and liver or kidney dysfunction (OR: 1.79, 95% CI: 1.19–2.69) were identified as predictors of DDIs. After adjusting for these variables in multivariate logistic regression analysis, the number of co-administered medications (OR: 1.34, 95% CI: 1.12–1.51) and cyclosporine as the main immunosuppressant drug (OR: 10.43, 95% CI: 6.24–17.42) were found to be independent predictors of DDI (Table 6).

DISCUSSION

To the best of our knowledge, no published study has so far considered this topic in kidney transplant recipients and screen all the medications which kidney transplant recipient were used for potential DDIs and factors that could prone these patients to experience potential DDIs. In the present study, 88% of patients had at least one class of D or X interaction. According to the results of Riechelmann, *et al*, systematic review on the epidemiology of PDDIs in oncology published up to April 2009, 12%–63% of oncology patients were exposed to PDDIs [18]. Nobovati, *et al*, in a systematic review on 34 published English- or Persian-language studies relevant to DDIs in Iranian population up to March 2013 showed that the median frequency of DDIs in outpatients and inpatients was 8.5% per prescription and 19.2%, respectively [16]. This wide variation in the frequency of DDIs can be attributed to the different study methodology (e.g., retrospective *vs.* prospective), screening and detection method of DDIs, and clinical setting (e.g., inpatient *vs.* outpatient). Regarding the method of DDIs screening and detection, we utilized Lexi-Interact software in this study. In comparing five common DDI software programs including Lexi-Interact, Micromedex Drug Interactions, iFacts, Medscape, and Epocrates by Kheshtie, *et al*, showed that Lexi-Interact and Micromedex had the best performances in terms of accuracy and comprehensiveness [21].

In our study, mechanism of more than 80% of all the detected DDIs was pharmacokinetics. This was in line with results from other clinical settings, such as HIV or cancer patients [19, 22-24]. Informing kidney transplant recipients about pharmacokinetic DDIs and considering the appropriate time for consuming medication can be effective in reducing the development of pharmacokinetic DDIs. Therapeutic drug monitoring (TDM) and dose

Table 6: Comparison between different demographic, clinical, and paraclinical characteristics of patients with and without identified drug-drug interactions (n=390).

Variable	Patients with DDI, (n=192)	Patients without DDI, (n=198)	Crude OR (95% CI) [p value]	Adj. OR (95% CI) [p value]
Sex				
Male, n (%)	124 (65)	141 (71)	0.74 (0.48–1.13) [0.161]	—
Female, n (%)	68 (35)	57 (29)		
Age (yrs)				
Mean±SD	46.0±14.1	42.5±14.1	1.02 (1.003–1.032) [0.017]	1.00 (0.98–1.02) [0.863]
Range	20–71	18–72		
Duration of immunosuppressive treatment (months)				
Median (IQR)	50.0 (83)	38.0 (56)	1.003 (1.000–1.007) [0.069]	—
Range	1–243	1–264		
Underlying disease				
Yes, n (%)	121 (63)	117 (59)	0.85 (0.56–1.27) [0.426]	—
No, n (%)	71 (37)	81 (41)		
Dialysis type				
Hemodialysis, n (%)	176 (92)	187 (95)	0.65 (0.29–1.43) [0.283]	—
Peritoneal dialysis, n (%)	16 (8)	11 (5)		
Duration of dialysis (months)				
Median (IQR)	12.0 (17.0)	11.5 (12.0)	1.006 (0.99–1.02) [0.311]	—
Range	0.0–96.0	0.0–120.0		
Donor type				
Non-relative living donor, n (%)	44 (23)	20 (10)	0.69 (0.52–0.90) [0.006]	0.75 (0.54–1.03) [0.075]
Relative living donor, n (%)	22 (11)	31 (16)		
Deceased, n (%)	126(66)	147 (74)		
Number of medications				
Median (IQR)	6.0 (3.0)	5.0 (3.0)	1.19 (1.08–1.31) [<0.001]	1.34 (1.19–1.51) [<0.001]
Range	3–16	0-17		
Immunosuppressive main agent				
Tacrolimus, n (%)	56 (29)	174 (88)	9.12 (5.70–14.60) [<0.001]	10.43 (6.24–17.42) [<0.001]
Cyclosporine, n (%)	132 (69)	15 (7)		
Others, n (%)	4 (2)	9 (5)		
Organ dysfunction				
Yes, n (%)	94 (49)	69 (25)	1.79 (1.19–2.69) [0.005]	1.46 (0.98–2.39) [0.134]
No, n (%)	98 (51)	129 (65)		

adjustment for certain immunosuppressant medications, such as calcineurin inhibitors and mammalian target of rapamycin (mTOR) inhibitors, accordingly, can prevent possible adverse events related to pharmacokinetic DDIs.

The most frequent detected class X DDI in our study was between cyclosporine and atorvastatin. Atorvastatin was in the drug list of more than one-quarter (26.67%) of patients recruited into the study. Cyclosporine can increase serum concentration of atorvastatin by inhibiting its metabolism via CYP3A4 and reducing hepatic uptake of atorvastatin by OAT-

P1B1-SLCO1B1. This could result in myopathy, rhabdomyolysis, leading to acute kidney injury. TDM for atorvastatin and dose reduction base on its serum concentration can be effective in preventing or reducing clinical complications of DDI but TDM for atorvastatin which should be done using high-performance liquid chromatography-mass spectrometry assays could be not available in many centers [25, 26]. Instead, some databases have recommended not to exceed the dose of atorvastatin more than 10 mg/day in patients receiving cyclosporine concomitantly [27] and most of the clinical trials used atorvastatin 10 mg/day in cyclosporine-based immunosuppressive regimens [28]. However, patients in our study received about twice as much as this daily dose of atorvastatin (mean±SD of 19.23±7.72 mg/day). This could increase the risk of myopathy, rhabdomyolysis, and consequently, acute kidney injury. Another possible approach to reduce these risks in kidney transplant recipient who need to take atorvastatin is to use tacrolimus instead of cyclosporine. The possible DDI between tacrolimus and statins is less severe compared to cyclosporine [29, 30].

In the current study, inhibition of Multidrug Resistance Associated Protein 2 (MRP2) and blocking the enterohepatic cycle of mycophenolic acid by cyclosporine was the most common mechanism of type D DDI. This can potentially lead to reduced bioavailability that consequently diminishes the efficacy of mycophenolic acid. Therefore, as this interaction is mentioned in latest transplantation protocols which cyclosporine could lower mycophenolic acid concentration and serum levels of the medication will increase when cyclosporine administration is discontinued, the daily dose maintenance of mycophenolic acid in kidney transplant recipients, receiving cyclosporine concurrently is about 500 mg more than that of tacrolimus recipients [31]. This DDI and reducing the daily dose of mycophenolic acid to about 500 mg should be taken into consideration when switching from cyclosporine to tacrolimus to minimize mycophenolic acid dose-dependent adverse effects, such as gastrointestinal disturbances and bone-marrow suppression [32-35]. Finally, according to the Kidney Disease-Improving Global Outcomes (KDIGO) guideline, mycophenolic acid and a calcineurin inhibitor (e.g., cyclosporine) are a part of maintenance triple immunosuppressive regimen in kidney transplantation [36]. It is a currently a well-known and acceptable combination in many transplant centers.

In this study, we observed that the immunosuppressive main drugs (tacrolimus *vs.* cyclosporine) as an independent associated factor developed DDIs. In the previous studies, it was stated that cyclosporine is vulnerable to more DDIs in comparison to tacrolimus [37, 38]. Cyclosporine has more inhibitory effects on liver enzymes that are responsible for drug metabolism (e.g., CYP3A4), and consequently interact more with medications that undergo hepatic metabolism [39]. Furthermore, cyclosporine can inhibit p-glycoprotein and might interact with substrates of this glycoprotein [40]. Tacrolimus might have other potential benefits over cyclosporine including less frequency of certain adverse reactions (e.g., hypertension, hyperlipidemia, gingival hyperplasia, and hirsutism) and more potent immunosuppressive effects [41-43].

Number of co-administered medications as another factor was significantly associated with DDIs. This finding is in line with other studies, particularly in conditions requiring complex treatment, such as cancer and emergency setting [18, 44, 45]. A systematic review conducted by Nabovati, *et al*, showed the significant association between DDIs and the number of co-administered medicines in an Iranian population [20]. According to the National Rational Drug Use Committee official report, the mean number of drugs per prescription in the outpatient setting in Iran was 3.16 and 3.05 in 2010 and 2011, respectively [46]. Kidney transplanted patients generally receive three medications as their maintenance immunosuppressive regimen. In addition, they usually have co-morbidities (e.g., previous or new-onset hypertension, hyperlipidemia, and diabetes mellitus) that needs to be treated with different medications [47, 48].

In our study, immunosuppressant medica-

tions involved 87% of detected DDIs. In addition, about half (49.1%) of all the detected DDIs were between two immunosuppressant medications. This highlights the importance of selecting an immunosuppressant with lower interaction potential (i.e., tacrolimus instead of cyclosporine). It is also logical to choose medication with more desirable interaction profile concomitant with immunosuppressant agents (e.g., fenofibrate instead of gemfibrozil, pravastatin instead of simvastatin, or pantoprazole instead of omeprazole).

Although the current study is the first one on potential DDIs amongst kidney transplant outpatients, to the best of our knowledge, it has its own limitations. This study was retrospective; thus, some information of patient's records like immunosuppressive medication serum level were not for all patients. Not considering herbal and over the counter drugs was another limitation. Other limitations are not including inpatients and comparing their DDI profile with outpatients, using only one database and software for screening and detecting DDIs, unknown real clinical consequence of detected DDIs due to the cross-sectional nature of the study design, recruiting patients from only two settings (center bias), and undetermined onset of detected DDIs since Lexi-Interact software (in contrast to Drug Interaction Facts and Micromedex Drug-Reax) generally does not support this data.

In conclusion, our data showed that about 90% of kidney transplant outpatients were exposed to at least one moderate or major DDI. More than 80% of the detected DDIs were pharmacokinetics. Interaction between cyclosporine + mycophenolic acid (32.3%) was the most frequent detected DDIs followed by cyclosporine + atorvastatin (11.3%). The number of co-administered medications and cyclosporine (as a major immunosuppressant agent) were significantly associated with DDIs. In fact, DDI is an inseparable and inevitable part of pharmacotherapy. However, physicians and pharmacist's awareness and vigilance regarding major DDIs is of great importance, especially in critical clinical settings such as kidney transplantation. Finally, it is noteworthy that although not all the detected DDIs led to clinical complications (e.g., treatment failure, adverse reaction, or overdose), but high prevalence of DDIs is an alarming sign for incidence of real interaction in outpatient kidney transplant recipients and it calls for health care member's attention.

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